UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/401,839	09/22/1999	MAURICE KENT GATELY	1803-247	5191

151 7590 06/12/2003

HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

EXAMINER
MERTZ, PREMA MARIA

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/401,839	Gately et al.
Examiner	**Art Unit**
Prema Mertz	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *1/23/03, 3/24/03*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *33-44* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *33-44* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/24/03 has been entered.

Claim objections

2. Claims 35-38 and 41-44 are objected to because of the following:

Claims 35 and 36 are objected to under 37 CFR 1.75 as being a substantial duplicates of claims 37 and 38, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP.. § 706.03(k).

Claims 41 and 42 are objected to under 37 CFR 1.75 as being a substantial duplicates of claims 43 and 44, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP.. § 706.03(k).

Claim Rejections - 35 USC § 102(e)

3. Claims 33-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Trinchieri et al. (US Patent No. 5,811,523).

This rejection is maintained for reasons of record set forth at page 5 of the previous Office action (Paper No. 5, 1/24/00) and on page 2 (Paper No. 15, 4/20/01).

The declaration by Dr. William R. Benjamin filed in Paper No. 23 (1/30/03) is insufficient to overcome the rejection of claims 33-44 based upon 35 U.S.C. § 102(e), as set forth in the last Office action because the showing in the declaration is ineffective to overcome the reference '523 patent. The arguments supplied in the declaration and arguments by Applicants in Paper No. 22 (1/23/03) are similar and will be addressed together by the examiner.

Applicants argue that they seek, pursuant to 37 C.F.R. *§§* 1.607 and 1.608(b) to provoke an interference between the instant application and U.S. Patent No. 5,811,523. However, contrary to Applicants arguments, the position of the Office is that the 35 U.S.C. 102(e) rejection over claims 33-44 as being anticipated by Trinchieri et al. (US Patent No. 5,811,523), is being maintained. The crucial issue here is that the priority date for US Patent No. 5,811,523, is 11/10/1988, which is the earliest application that describes partial amino acid sequences of the protein and the biological activity of the protein. Furthermore, the declaration of Dr. William R. Benjamin is non-persuasive because it fails to demonstrate that (1) the '523 patent is not entitled to its earliest filing date of 11/10/88 and (2) diagnostic and therapeutic uses of the claimed antibodies are not a specific utility. Therefore, an interference with U.S. Patent No. 5,811,523 and the instant application cannot be declared at this time.

The request pursuant to 37 C.F.R. §§ 1.607 and 1.608(b) is being held in abeyance. The issue here is for Applicants to obviate the 35 U.S.C. 102(e) rejection. Applicants argue that only by using special techniques was it possible for Applicants to generate the antibodies that specifically react with the 30-35 kD subunit (Example 14, pages 79-80). Applicants also argue that none of the 20 monoclonal anti-CLMF antibodies produced from immunization with partially purified 75 kD heterodimeric CLMF bind to the 30-35 kD subunit. In support of this conclusion, Applicants have cited D'Andrea et al and Chizzonite et al., which are scientific publications from 1991.

Applicants argue that the results in D'Andrea et al show that antibodies generated against recombinantly produced NKSF heterodimer fail to react with the 30-35 kD NKSF subunit and react only with the NKSF 40 kD subunit. However, contrary to Applicants arguments, the reference discloses that the C2 and C3 series of mABs generated using *E. coli*- derived p40 chain as antigen , react with both *E. coli*-derived and Cos-derived p40 as well as with CHO-derived p70 (see page 1390, column 1, see first full paragraph, specifically lines 9-13). The C8 series of antibodies, generated using as antigen Cos-derived p40 react with Cos-derived p40 and CHO-derived p70 but nor *E. coli* -derived p40 (see page 1390, column 1, lines 13-16). The reference also discloses that antibodies generated using as antigen *E. coli*- derived p35 react with E. coli derived p35 and with the p70 heterodimer but not with the p40 preparation (see page 1390, column 1, lines 19-22). The reference discloses that the antibodies against CHO-derived p70 react with p40 but no data is shown and the reactivity of the antibody with p35 is not mentioned,

which does not reach the conclusion that there is no reactivity of this antibody with the p35 subunit (see page 1390, column 1, lines 17-19).

With respect to the Chizzonite et al reference, Applicants argue that the results presented demonstrate that using purified NKSF resulted only in generating antibodies which specifically bind the 40 kD subunit (page 1554, left column). However, contrary to Applicants arguments, the reference discloses that the anti-IL-12 serum and anti-IL-12 mAb had a preference for the 40 kD subunit (see page 1554, column 1, first three lines of second full-para). The reference does not teach away from the conclusion that the anti-IL-12 serum can also react with the p35 subunit i.e. that antibodies to the p35 subunit can also be obtained. A lot more hybridomas may have to be screened to get anti-IL-12 antibodies that react with the p35 subunit. Furthermore, Chizzonite et al point out that the apparent preference for antibodies directed against the 40 kD subunit, may be because significant amounts of free 40 D subunit are present in purified IL-12 samples which can bias toward identification of antibodies against the 40 kD subunit (see page 1555, left column). Chizzonite et al also reports that apparently antibodies against the 35 kD subunit arise only after "multiple immunizations" as opposed to antibodies against the 40 kD subunit which arise very rapidly (see page 1555, left column, last para). If multiple immunizations was the state of the prior art at the time of the earliest priority date of the Trinchieri '523 patent, the initial Trinchieri application (filing date, 11/10/88) was enabling for antibodies to the 35 kD subunit because not only the disclosure of the specification but the state of the prior art at the time an application is filed, is considered in determining whether a specification is enabling. The state of

the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification. Therefore, the state of the prior art evaluated at the time of the earliest Trinchieri application supports the conclusion that multiple immunizations with the 75 kD heterodimer would have resulted in the production of antibodies to the p35 subunit and the application would have been enabling for the claimed Trinchieri '523 invention.

Applicants argue that one skilled in the art upon observing that immunized animals produced a sufficient titer of polyclonal antibodies that specifically react wit IL-12 would have terminated the immunization schedule and sacrificed the animal. However, contrary to Applicants arguments, if the Western blot analysis demonstrated that the polyclonal antibodies obtained reacted with the p40 subunit, one of skill in the art at the time of the earliest Trinchieri application, would have been motivated to further immunize the animal with the p70 heterodimer to obtain antibodies to the p35 subunit or to screen more hybridomas to obtain monoclonal antibodies to the p35 subunit because the state of the art at the time of the invention was such that working examples to demonstrate such were not required in the specification as filed.

Applicants argue that from the disclosure of '945 application, there would have been no utility in purifying IL-12 because the IL-12 heterodimer and the free 40 kD subunit would have not been distinguished. However, contrary to Applicants arguments, the '945 application states that the NKSF polypeptides are used in the development of monoclonal and polyclonal antibody

generation which antibodies are to be used diagnostically or therapeutically. There is no mention in the disclosure of the use of the antibodies to selectively purify IL-12 heterodimer from the free 40 kD subunit, as argued by Applicants. Therefore, Applicants arguments that none of the antibodies in the '945 application would have been able to selectively purify IL-12 heterodimer from free 40 kD subunit are unpersuasive because the use of the antibodies as disclosed in the '945 application were for diagnostic or therapeutic purposes, not to purify the IL-12 heterodimer. The state of the art at the time of the '945 application was that antibodies could be generated against the p70 heterodimer or p40 alone. Furthermore, as discussed above, multiple immunizations with the p70 heterodimer would have resulted in the production of antibodies to the p35 subunit.

With respect to Applicants arguments that the Trinchieri '945 and '817 applications fail to describe any specific diagnostic or therapeutic use for antibodies that react wit NKSF, this argument is also unpersuasive. The Federal Circuit has repeatedly held that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Nevertheless, in the instant case not everything necessary to practice the claimed invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the knowledge and skill in the art. Section 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most clearly

connected". The amount of guidance or direction present refers to information in the application that teaches how to make or use the invention, the amount of guidance or direction needed to enable the invention being inversely related to the amount of knowledge in the state of the art. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970).

In the instant case, the relative skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the Trinchieri '945 and '817 applications were filed, was such that it was unnecessary for the specification to disclose what was well-known in the art and already available to the public (i.e. the diagnostic and therapeutic use for antibodies that react with NKSF). A lot was known in the prior art about the nature of the invention and details as to how to make and use the invention were not required in order for the instant specification to be enabling.

Applicants argue that a publication by Stern et al. (1990) which discloses polyclonal and monoclonal antibodies to CLMF and the 40 kD subunit anticipates claims 1, 2, 4 and 6 of the '523 patent but is not prior art to Applicants' captioned application. However, contrary to Applicants arguments, the Stern et al. publication is not prior art to the '523 patent because the earliest priority date of the '523 patent is 11/10/1988 due to filing of the '945 application.

With respect to claims 4, 5, of the Trinchieri '523 patent, Applicants argue that the '523 patent lacks written description of any "murine antibody" or "human antibody" since there is no mention of such subject matter in the patent. However, contrary to applicants arguments, the making of humanized as well as murine antibodies were well known in the art at the time of

filing of Trinchieri's earliest application (11/10/88) and standard techniques would have been used to generate such antibodies. The Examiner has cited Jones et al. (1986), Liu et al. (1987), Verhoeyen et al. (March, 1988) and Tan et al (1985) for the proposition that human and murine antibodies could be constructed without having to resort to undue experimentation and were not beyond the state of the art at the time the '817 and '945 applications were filed. Therefore, the '817 and '945 Trinchieri applications are enabling for murine and human antibodies to IL-12 as claimed in the '523 patent.

Applicants argue that the '945 application of Trinchieri discloses six peptides each ranging from five to eight amino acid residues in length ('945 application, page 27, lines 5-10). Applicants also argue that peptides 4, 5 and 6 correspond to the 35 kD subunit and that in the '817 application of Trinchieri, at positions 7 and 11 there were 2 mistakes in this amino acid sequence (see Benjamin Dec. Para 21). However, contrary to Applicants arguments, fragment number 6 (peptide 6) in the '945 application is a seven amino acid peptide which according to Harlow and Lane (cited by Applicants) as a synthetic peptide would suffice to produce antibodies to a protein containing that sequence. Therefore, even though the '945 application does not specifically teach the presence of a 35 kD subunit, the recitation of the seven amino acid peptide present in the 35 kD subunit, would suffice to produce antibodies to the 35 kD subunit.

In conclusion, since the specification of Trinchieri's earliest application 07/269,945 filed 11/10/88, does disclose a single credible, specific or substantial utility for the instant antibodies to the CLMF polypeptide, Applicants arguments with respect to why this earliest application fails

to support enablement and/or utility of the subject matter of the count, are found to be non-persuasive.

Claim Rejections - 35 USC § 103

4. Claims 33-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trinchieri et al. (U.S. Patent No. 5,811, 523).

This rejection is maintained for reasons of record set forth at pages 3-4 of the previous Office action (Paper No. 5, 1/24/00) and on page 3 (Paper No. 15, 4/20/01) and for the reasons as set forth in paragraph 3 above.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 305-3014 or (703 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 746-5300.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz

Prema Mertz Ph.D.

Primary Examiner
Art Unit 1646
May 19, 2003